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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,894	03/01/2002	Elizabeth J. Ackermann	ISPH-0573	1283

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LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,894	ACKERMANN ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *18-33 and 35-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-17 and 34 in the Paper filed 10-09-03 is acknowledged. The traversal is on the ground(s) that all of the claims are drawn to the single feature of an antisense compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding a novel apoptotic bcl-2-related protein. This is not found persuasive because as stated in the prior Office Action the technical feature shared between groups I and II do not appear to be a "special technical feature," since this feature does not make a contribution over the prior art. Chao et al. discloses an oligonucleotide that is an antisense oligonucleotide primer to *mcl-1* mRNA of 29 nucleotides in length, and having the sequence: 5'-GCGTCGACAGGCTATCTTATTAGATATGC-3', see page 4884, 2nd column, paragraph 3. Absent evidence to the contrary, since the antisense oligonucleotide primer of Chao et al. meets all the structural limitations of the product according to invention I, the teachings of Chao et al. is considered to anticipate the technical feature that is shared between groups I and II. Therefore, lack of unity of invention is considered proper in this particular instance since Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 18-33 and 35-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Paper filed 10-09-03.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 15-17, and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The pharmaceutical composition comprising an antisense compound targeting the expression of a novel anti-apoptotic bcl-2-related protein and methods of treating a patient with a disease associated with a novel anti-apoptotic bcl-2-related protein comprising administering of said composition referred to in these claims implies *in vivo* applicability for enablement purposes. There are no general guidelines for successful *in vivo* delivery of antisense/ribozyme compounds currently known in the art, nor are such guidelines provided in the specification as filed. Crooke (1998), states that "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". According to Branch (1998), the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNAs and their association with cellular proteins can render target sites totally inaccessible *in vivo*. Antisense therapy is a highly unpredictable and field and the skill in the art is high. See Gura which states: "The uncertainty about what antisense drugs are doing inside the body has caused some experts in the field to argue that clinical trials have begun far too soon". Stanley Crooke says, in Antisense '97, "Never in the history of drug discovery and development

has anyone attempted to correlate the pharmacokinetics with any class of drugs with cellular uptake *in vitro*".

Therefore, the specification does not describe the pharmaceutical composition comprising an antisense compound targeting the expression of a novel anti-apoptotic bcl-2-related protein and methods of treating a patient with a disease associated with a novel anti-apoptotic bcl-2-related protein comprising administering of said composition according to these claims in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. These conclusions are based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with secondary effects such as treating a condition related to the level of expression a novel anti-apoptotic bcl-2-related protein in a patient, and the lack of guidance in the specification as filed in this regard.

The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (treatment leading to the amelioration of conditions associated with the expression of a novel anti-apoptotic bcl-2-related protein) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-11, 13, and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al., Chao et al, and Shin et al., in view of Branch (1998), Monia et al., and Agrawal et al.

Green et al. teach a method for enhancing apoptosis in cells by treating the cells with antisense oligonucleotides that hybridize to a known anti-apoptotic gene such as bcl2 and bcr-abl (col.2, lines 50-67). Green et al. designed antisense oligonucleotide of 18 nucleotides in length targeting bcr-abl (col 2 lines 65-67). Chao et al. teach the use of antisense constructs in the inhibition of novel bcl-2 anti-apoptotic gene *mcl-1* leading to an induction of apoptosis in TF-1 myeloid progenitor cells (p. 4893). Shin et al teach that A1 (GRS or bfl-1) is a member of the bcl-2 related gene family, possessing significant homology to bcl-2, and that it functions in the regulation of apoptosis as an inhibitor of apoptosis (p. 7).

Neither reference above, specifically teach the design of antisense oligonucleotides of 8 to 30 nucleotides targeting *mcl-1* or human A1. Additionally, the above references do not teach wherein the disclosed antisense oligonucleotides comprise at least one modified sugar moiety, at least one modified nucleobase, wherein the antisense oligonucleotide is a chimeric oligonucleotide, or wherein said antisense compound is in a pharmaceutically acceptable carrier, and further comprising a colloidal dispersion system.

Branch teach that in order to maximize target site specificity the length of antisense oligonucleotides should be 17 base pairs or longer, since sequences of 17 base pairs or more would have a high probability of occurring only once in the haploid human genome. However, increasing the length of the oligonucleotide beyond this minimum would likely stabilize non-specific binding to mismatch sequences (p. 47, para. 5-6).

Monia et al. teach the design of antisense oligonucleotides comprising various modifications, including phosphorothioate modified internucleoside linkages (col. 8, line 41-43), 2'-O-methoxyethyl sugar modifications (col. 10, line5), 5-methylcytosine modified nucleobase (col. 10, line 31-32), and wherein the antisense oligonucleotide is a chimeric oligonucleotide (col. 11, line 51). The modified or substituted oligonucleotides of Monia et al. are preferred over native (unmodified or unsubstituted) forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced binding to target and increased stability in the presence of nucleases (col. 8, lines 2-6). Additionally, Monia et al. teach the use compositions comprising antisense oligonucleotides and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system in order to enhance the stability of oligonucleotides introduced into cells and to target oligonucleotides to a particular tissue or cell (col. 15, lines 19-41).

Agrawal provides motivation for designing antisense oligonucleotides targeting various regions of a target mRNA, including for example the coding region and the 5'-UTR and 3'-UTR of a target mRNA. According to Agrawal et al. "[I]t is considered preferable, therefore, to screen a number of oligonucleotides that encompass different regions on RNA to identify a set of optimal target sites, including the 5'- and 3'-untranslated regions (UTRs), initiation codon site,

coding region and intron-exon junctions." (page 77, 1st para.) Additionally, Agrawal et al. generally states (regarding the feasibility of utilizing antisense technology), "antisense technology has become an essential laboratory tool to study and understand the function of any newly discovered genes in recent years."

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of to produce the compounds and compositions according to the present invention. One of ordinary skill in the art would have been motivated to modify the teachings of Green et al., Chao et al, and Shin et al., in view of Branch (1998), Monia et al., and Agrawal et al. to make the antisense compounds targeting novel bcl-2 anti-apoptotic genes *mcl-1* or human A1 according to the present invention. One of ordinary skill in the art would have been motivated to design antisense compounds to comprise about 17 nucleobases in length or more, because antisense compounds of about 17 nucleobases in length would enhance target site specificity for the antisense to its target mRNA (Branch). One of ordinary skill in the art would have been motivated to further modify the antisense compounds of Chao et al. and Shin et al. to comprise phosphorothioate modified internucleoside linkages, 2'-O-methoxyethyl sugar modifications, 5-methylcytosine modified nucleobases, or wherein said antisense compound is a chimeric compound, because according to Monia et al. these modifications would enhance the cellular properties of antisense compounds as compared to unmodified antisense compounds. Moreover, one of ordinary skill in the art would have been motivated to design compositions comprising the antisense compounds according to the present invention and a pharmaceutical carrier or diluent, and further comprising a colloidal dispersion system because Monia et al. teach that compositions designed according to this manner would enhance the stability of

oligonucleotides introduced into cells and would help to target oligonucleotides to a particular tissue or cell.

Moreover, one of ordinary skill in the art at the time the invention was made seeking methods to regulate apoptosis in a cell would have been motivated to design antisense oligonucleotides to target anti-apoptotic genes, because Green et al. and Chao et al. teach the ability of antisense constructs to inhibit the expression of *mcl-1* in TF-1 myeloid precursor cells, wherein *mcl*-1 inhibition results in the triggering of apoptosis in these cells. Additionally, one of ordinary skill in the art seeking to further understand the role of novel anti-apoptotic bcl-2 related genes, would have been motivated to design antisense oligonucleotides targeting the mRNA encoding the *mcl-1*, and human A1 genes since according to Agrawal, if the sequence of a gene is known, designing antisense oligonucleotides to target that gene would allow the ordinary skilled artisan to further explore and understand the function of that particular gene.

Therefore, the invention as a whole would have been *prima facie* obvious over Green et al., Chao et al, and Shin et al., in view of Branch (1998), Monia et al., and Agrawal et al. at the time the invention was made.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-16 are rejected under the judicially created doctrine of obviousness-type double-patenting as being unpatentable over claims 1-14, and 21-40 of U.S. Patent No. 6,001,992. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claim(s) 1-11 and 13 are generic to all that is recited in claim(s) 1-12, and 21-40 of U.S. Patent No. 6,001,992. That is, claim(s) 1-12 and 21-40 of U.S. Patent No. 6,001,992 falls entirely within the scope of instant claim(s) 1-11 and 13 or, in other words, claim(s) 1-11 and 13 are anticipated by claim(s) 1-12 and 21-40 of U.S. Patent No. 6,001,992. Specifically, the issued claims are drawn to antisense compounds 8 to 30 in length targeted to either SEQ ID NO: 1 or SEQ ID NO: 18, nucleic acid molecules encoding novel anti-apoptotic bcl-2 related proteins, and the instant claims 1-11 and 13 are generic to all that is recited in the issued claims.

Instant claims 12 and 14 are drawn to antisense compounds targeted to novel anti-apoptotic bcl-2 related proteins, wherein the antisense oligonucleotide comprises SEQ ID NO: 3-

16, or SEQ ID NO: 22-23, 31, 35 or 36. Issued claim 21 an antisense compound up to 30 nucleobases in length targeted to a nucleic acid encoding human A1 wherein the antisense compound comprises at least 8 nucleobases of SEQ ID NO: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, and inhibits expression of said human A1. Issued claim 31 recites an antisense compound up to 30 nucleobases in length targeted to nucleic acid encoding human mcl-1 wherein the antisense compound comprises at least 8 nucleobases of SEQ ID NO: 22-23, 31, 35 or 36. The antisense compounds of instant claims 12 and 14 are obvious variants of issued claims 21 and 31 since the instant claims are limited to compounds that are 8 to 30 nucleobases in length, therefore the claims encompass compounds that are up to 30 nucleobases in length and comprise a sequence according to SEQ ID NO: 3-16 or SEQ ID NO: 22-23, 31, 35 or 36.

Instant claims 15-16 are drawn to pharmaceutical compositions comprising an antisense compound of 8 to 30 nucleobases in length targeting a novel anti-apoptotic bcl-2-related protein, and a pharmaceutically acceptable carrier or diluent, and further wherein said composition comprises a colloidal dispersion. Issued claims 13-14 are broadly drawn to compositions comprising antisense compounds targeting SEQ ID NO: 1 or 18, and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion. Instant claims 15-16 are an obvious variant of issued claims 13-14 because the term "pharmaceutical" as recited in the instant claims merely represents an intended use for the claimed compositions, and the issued claimed compositions also comprise the same components as the instant compositions except that the antisense compounds of the instant claims are broader in scope than those of the issued claims.

Notice of References Cited

9. All references cited in this action, with the exception of the Agrawal et al., Monia et al., and US Patent No. 6,001,992, were all cited during the prosecution of parent Application 09/226,568.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE